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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,491	02/05/2002	Philip Kusk	8969-029	4096
21874	7590	08/10/2005	EXAMINER	
EDWARDS & ANGELL, LLP			SWITZER, JULIET CAROLINE	
P.O. BOX 55874			ART UNIT	
BOSTON, MA 02205			PAPER NUMBER	
			1634	
DATE MAILED: 08/10/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/889,491

Applicant(s)

KUSK, PHILIP

Examiner

Juliet C. Switzer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 May 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 25-37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 25 is/are allowed.
- 6) ☒ Claim(s) 26-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/6/05 has been entered.

2. Claim 25 is allowed. In light of the allowable subject matter, all claims which require the assay of combinations of polymorphisms that include those listed in claim 25 are allowed. All pending claims are rejoined and examined herein. New rejections are set forth to address the rejoined claims.

### ***Sequence Rules***

3. The paper copy of the sequence listing filed 2/22/05 has been entered into the specification. This application is in compliance with the sequence rules.

### ***Claim Rejections - 35 USC § 112-New Matter***

4. The rejection of claims 25, 29, and 30 under 35 U.S.C. 112, first paragraph, for new matter is withdrawn in view of the amendment to claim 25 removing the new matter.

### ***Claim Rejections - 35 USC § 112, Second Paragraph***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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6. The rejection of claims 25, 29, and 30 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendments to the claims to overcome the rejection. New rejections are set forth to address the rejoined claims.

7. Claims 29-30, 33-34, and 36-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 29, the phrase "said gene promoter" is indefinite because it is not clear if it is referring to the gene promoter of the previously set forth bone sialoprotein gene promoter or the previously set forth promoter of said matrix gla protein gene. Amendment of the claim to recite, for example, "of either or both of said gene promoters of said individual" will overcome this rejection. Claim 30 depends from claim 29 and is indefinite for the same reason. If applicant amends claim 29 as suggested, applicant it is suggested that applicant also amend claim 30 to recite "said amplified portion or portions."

In claim 33, the phrase "said gene promoter" is indefinite because it is not clear if it is referring to the gene promoter of the previously set forth bone sialoprotein gene promoter or the previously set forth promoter of said osteopontin gene or the previously set forth matrix gla protein promoter. Amendment of the claim to recite, for example, "of one or more of said gene promoters of said individual" will overcome this rejection. Claim 34 depends from claim 33 and is indefinite for the same reason. If applicant amends claim 33 as suggested, applicant it is suggested that applicant also amend claim 34 to recite "said amplified portion or portions."

In claim 36, the phrase "said gene promoter" is indefinite because it is not clear if it is referring to the gene promoter of the previously set forth bone sialoprotein gene promoter or the

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previously set forth promoter of said osteopontin gene or one of the other previously set forth gene promoters. Amendment of the claim to recite, for example, "of one or more of said gene promoters of said individual" will overcome this rejection. Claim 37 depends from claim 36 and is indefinite for the same reason. If applicant amends claim 36 as suggested, applicant it is suggested that applicant also amend claim 37 to recite "said amplified portion or portions."

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The rejection of claims 25, 29, and 30 under 35 U.S.C. 112, first paragraph, which addressed the GenBank accession numbers in the claims is WITHDRAWN in view of the removal of these from the claims.

10. Claims 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is written to address the portions of the rejoined claims that assert relationships between particular polymorphic alleles and phenotypes.

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Claim 26 recites the further assay of a polymorphism at position 242 of the matrix gla protein gene (SEQ ID NO: 26) and “associating the presence of said adenine in said sequence with a predisposition to a higher rate of loss of bone mass than when cytosine is present.”

Claim 27 recites the further assay of a polymorphisms at positions 1825 and 520 of the osteopontin gene (SEQ ID NO: 27) and “associating the presence of said adenine in said sequence spanning base pair 520 with a predisposition to a higher rate of loss of bone mass than when guanine is present, and the presence of said thymine in the sequence spanning base pair 1825 with a predisposition to a lower bone mass than when cytosine is present.”

Claim 28 recites the further assay of a polymorphism at position 163 of the osteoprotegerin gene (SEQ ID NO: 28) and “associating the presence of said guanine in said sequence with a predisposition to a lower peak bone mass than when adenine is present.”

Additional claims 32 and 35 also recite these same further assays but represent different combinations with regard to which polymorphisms are actually assayed in combination with those recited in claim 25.

Claim 25 is allowed. The remaining claims are either dependent from claim 25 or include all of the same limitations of claim 25 with regard to the bone sialoprotein gene. The rejected claims, however, include these additional cited relationships between polymorphisms in additional genes and either peak bone mass or rate of loss of bone mass. The nature of the invention with regard to the rejected claims, thus, requires that the polymorphisms in the bone sialoprotein gene be associated with lower peak bone mass, but also require that the additional recited relationships be supported by the specification, as they are recited in the plain language in the claims. Thus, in this case, the independent claim 25 is enabled by the specification, but the

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claims which depend from this claim but recite additional relationships between polymorphisms and phenotypes are not enabled by the specification for the reasons set forth in this rejection.

### **Nature of the Invention**

The invention is concerned with providing a method for assessing an individual's predisposition to a lower peak bone mass via the genotyping of the promoter of the bone sialoprotein gene, and then further genotyping polymorphisms in different genes and associating these with either a predisposition to lower peak bone mass or rate of bone mass loss. Thus, the practice of the method relies on the showing of an association between a particular genotype and a particular calcification condition status.

### **Breadth of the claims**

The claims are narrow with regard to the recited associations between particular polymorphic variants and associations.

### **Teachings in the Specification and Working Examples**

The specification provides two novel polymorphisms within the 5' untranslated region of a gene taught by Kim *et al.* and referred to as the human bone sialoprotein promoter sequence, see GenBank L24756. Within this sequence, applicant identified polymorphisms at positions 1496 (A→G) and 1869 (G→A) wherein the first version is the version present in the published sequence and the second allele is the alternate allele identified by applicant (p. 7, lines 21-30). The specification refers to these variations as BSP-A1496G and BSP-G1869A, respectively.

The specification teaches an A→C polymorphism at position 242 of the matrix gla protein gene as set forth in SEQ ID NO: 26. The polymorphism is referred to in the specification as MGP-C242A.

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The specification teaches an A→G polymorphism at position 520, and a C→T polymorphism at position 1825 of the human osteopontin gene as set forth in SEQ ID NO: 27. The polymorphisms are referred to in the specification as OPN-G520A and OPN-T1825C.

The specification teaches a G→A polymorphism at position 163 of the osteoprotegerin gene as set forth in SEQ ID NO: 28.

In example 1 of the specification (beginning on page 22), applicant teaches the screening of the DNA from 133 women for the polymorphisms in the bone sialoprotein promoter sequence, in the matrix gla protein gene and in the osteopontin gene, via amplification of fragments of DNA and restriction digestion. A comparison of allele frequencies versus measures of bone mineral content and bone density was made using statistical analysis, the results are given in Table 2, page 31. The example demonstrates that there is a significant association between the bone sialoprotein promoter sequence polymorphisms and bone mass as represented by bone mineral content and bone mineral density measurements (p. 31). Specifically, patients with the “A” allele at 1469 and/or the “G” allele at 1869 are more likely to have higher bone mass than patients with the opposite alleles (p. 31-32). Notably, within this table, however, there is no finding of a significant difference between bone mineral content (BMC) or bone mineral density (BMD) for the polymorphisms in the MGP or OPN genes, namely, for these two genes the statistical analysis resulted in the finding that the means are statistically the same between the two test groups using a t-test. Regarding these MGP and OPN, the specification states that these polymorphisms are not suitable for a prediction of BMC or BMD (p. 32). Referring to Figures 5 and 6, however, applicant asserts that the MGP-C242A and OPN-G520A may be associated with rate of bone loss, based on the shape of the curves presented in figures 5 and 6. However, no

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statistical analysis was preformed, and upon review of the figures, it is noteworthy that at each point on the graphs the standard deviations of the individual data points overlap, suggesting that the values at each point are not significantly different from one another. Further, for the MGP polymorphism, the % difference between the two genotypes over time gets smaller in the last time period, suggesting that perhaps the difference in the rate of bone loss may be decreasing. Thus, the figures do not provide a basis for drawing conclusions regarding the effect of the genotypes on rate of bone loss, since it is not clear from the data given if the trends observed are significant trends. Figure 8 shows a similar comparison for alleles of the OPN-T1825C polymorphism. Again, in this case the means appear to be so close to one another so as to not represent statistically different values. Thus, the figure does not support the assertion in the claims that this polymorphism is associated with bone mass.

The osteoprotegerin gene polymorphism is assayed in example 2, beginning on page 35. The specification teaches that the polymorphism is significantly associated with a difference in bone mineral content, and that when considered either of the two BSP polymorphisms is associated with both BMC and BMD. Thus, claim 28 is enabled insofar as it depends from claim 25, but insofar as it depends from claim 26 which recites a relationship between matrix gla protein promoter polymorphism and predisposition for higher rate of bone mass loss.

#### **State of the prior art and Level of unpredictability**

The prior art is silent with regard to the assertions set forth in the rejected claims.

However, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay

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identifies polymorphisms, it is unpredictable whether any such polymorphisms (such as the two recited in the instant claims) would be associated with any phenotypic trait, such as a disease state or a physiological state. The instant specification demonstrates this unpredictability by demonstrating that the BSP polymorphisms are associated with peak bone mass but not with rate of bone loss. The prior art further exemplifies such unpredictability. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the  $\beta$ -globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma ( $p=0.294$ ). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed that the two polymorphisms in the promoter of a human bone sialoprotein gene are associated with peak bone mass, the remaining relationships set forth in the claims are highly unpredictable. Thus, the claimed method directed towards the assessment of a predisposition to a selected calcification condition status requires the knowledge of unpredictable and potentially non-existent associations between the instantly disclosed polymorphisms and additional calcification condition statuses.

### **Quantity of Experimentation**

The practice of the claimed invention commensurate in scope with the instant claims would require a high degree of experimentation to associate the disclosed polymorphisms with any or all calcification condition statuses. With respect to the disclosed polymorphisms within the bone sialoprotein gene, the practice of the claimed invention would require extensive further work to determine which calcification conditions can be predicted using even these polymorphisms. That this work would be unpredictable is exemplified in the specification which demonstrates that while the two disclosed polymorphisms in the bone sailoprotein gene may be predictors of bone mass within the tested population, they are not predictors of the rate of bone loss.

### **Conclusion**

Thus, having considered each of these factors, namely the breadth of the claims, the high level of unpredictability in the related art, the lack of guidance in the specification and the prior art, and the high quantity of experimentation, it is concluded that it would require undue

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experimentation to practice the claimed invention commensurate in scope with the instant claims.

**Response to Remarks**

The remarks regarding the previously set forth rejections are moot in view of the withdrawal of these rejections p. 13-19 of the response.

The interview summary is complete. Applicant's statements regarding potential enablement for the amended claims is addressed in the enablement rejection herein.

***Conclusion***

11. Claim 25 is allowed.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.


The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Juliet C. Switzer  
Primary Examiner  
Art Unit 1634

August 4, 2005